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ORIGINAL ARTICLE

Clinical manifestations and progression of IgM mesangial nephropathy: a single center prospective

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ABSTRACT

Out of 732 renal biopsies performed from 1988 to 1995 in Queen Elizabeth Hospital, 65 patients (8.9%, 43 male, 22 female) were diagnosed to have IgM mesangial nephropathy (IgMN). The mean age of the patients was 35 ±2 years. The clinical manifestations and progression of IgMN were studied in 39 of these 65 patients. The initial manifestations of the disease included nephrotic syndrome in 18 patients (46%), proteinuria and hematuria in nine patients (23%), non-nephrotic proteinuria in 11 patients (28%) and isolated hematuria in one patient (3%). The nephrotic syndrome was steroid-responsive in 16 of the 18 patients (89%) and six of them (33%) were steroid dependent. Two of the 11 (18%) patients in the isolated proteinuria group had a progressive deterioration in renal function. The renal function of the patients presented as hematuria with or without proteinuria remained stable during the follow-up period. We concluded that IgMN appeared to be a heterogeneous disease. Further studies on the classification and treatment are warranted in this group of patients.

Key words: Glomerulonephritis, Proteinuria, Renal failure

中文摘要

我們於 1988 年至 1995 年期間在伊利沙伯醫院進行了 732 例腎活檢，當中有 65 例(佔總數的 8.9% ，其中 43 例男性， 22 例女性)被診斷患有 IgM 系膜性腎病(IgMN)。本組病例的平均年齡為 35 ±2 歲。我們對這 65例患者中的39例進行了臨床表現與轉歸的研究。本病開始的臨床表現包括腎病綜合癥有18例(46%)、蛋白尿伴血尿有九例(23%)、非腎病性單純性蛋白尿有11例(28%)、單純性血尿有一例(3%)。在18例(89%)的腎病綜合癥患者中，有16例對激素治療有效，其中六例(33%)對激素依賴。在11例單純性蛋白尿者，其中兩例呈進行性腎功能減退。單純性血尿或血尿伴蛋白尿者在隨訪期間腎功能仍然穩定。我們的結論是：IgM 系膜性腎病似乎是一種異源性疾病。仍有必要對本症的分類與治療作進一步研究。

INTRODUCTION

IgM mesangial nephropathy (IgMN) was first described by Cohen et al (1) and Bhasin et al (2) in 1978. The glomerular lesion of IgMN is defined by its immunopathologic features (3): the presence of IgM as the sole or dominant immunoglobulin in glomerular mesangial regions in a diffuse and generalized distribution. The light microscopic manifestations are those of mild to moderate expansion of the mesangial regions, sometimes associated with increase in mesangial cellularity. Capillary walls and basement membrane are thin and delicate. Ultrastructural examination discloses the presence of typical electron dense mesangial deposits in approximately 50% of the biopsies (1). The remaining patients displayed ill-defined deposits or do not exhibit any recognizable ones. In patients with heavy proteinuria, effacement of epithelial foot processes was found (1,2, 4).

Since the report of Cohen and Bhasin, there has been considerable debate on the existence of this clinical entity and its prognostic significance. The response to steroid

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therapy and the long-term prognosis of this condition varied from studies to studies (4-9). Some investigators showed that patients with IgMN had a higher incidence of steroid dependency and responded partially to cyclophosphamide (5). Other investigators found that there was no difference between the groups with or without IgM deposits (6-8). Herein we studied retrospectively the prevalence, the different clinical manifestations, the progression and prognosis of IgMN in our locality.

METHODS

We reviewed all the renal biopsies done between January 1988 to June 1995 in our hospital retrospectively. The indications of renal biopsy were unexplained renal dysfunction and/or proteinuria more than 1 g/day and isolated hematuria. The renal biopsy specimens were examined by light-microscopic (LM) and immunofluorescence (IF) methods using standard techniques and electron microscopy. Paraffin sections for LM were stained by the hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome and periodic acid-silver methenamine methods. Direct IF studies were carried out using monospecific antisera against the heavy chains of human IgG, IgA and IgM and against C3, C4, C1q and fibrinogen. Patients who were diagnosed to have IgM nephropathy were treated initially with prednisolone 30 mg/day to 40 mg/day, and received treatment for at least 4 months. Patients were classified as steroid responsive if there was complete remission of proteinuria during treatment and had persistent remission for at least 2 months after termination of treatment. Patients were classified as steroid-dependent if they had complete remission during steroid therapy but recurrence when the dosage was reduced below a critical level or relapse within 2 months after discontinuation of therapy. They were classified as steroid resistant if they had no remission of proteinuria after 4 months of therapy. The clinical progression of the renal disease and the response to treatment were analyzed.

RESULTS

All together, there were 732 biopsies performed in the study period. Sixty-five patients (8.9%) were diagnosed to have IgMN. There were 43 males and 22 females and the mean age was 35 ±2 years. Twenty-six patients defaulted follow-up, making only 39 patients available for the study of the progress of the disease. Of the 39 patients, 18 (46%) presented as nephrotic syndrome, 11 (28%) presented as isolated proteinuria, nine (23%) presented as mixed proteinuria and hematuria and one (3%) as isolated hematuria (Table 1).

Table 1. Clinical data on patients with IgMN at presentation.

Clinical manifestation	NS	PU	PUH	H	All patients
Number of patients	18	11	9	1	39
Males/Females	15/3	9/2	3/6	1/0	28/11
Mean age (years)	26 ±10	42 ±16	44 ±11	30	35 ±2
Mean serum creatinine (μmol/L)	99 ±18	117 ±63	88 ±26	76	100.9
Mean proteinuria (g/day)	12.6 ±7	1.9 ±1.5	2.2 ±1.7	0.05	6.9
Median % of sclerosed	0	25	5	0	
Glomeruli on biopsy	(0)	(0-40)	(0-20)		

NS = Nephrotic syndrome; PU = Proteinuria; PUH = Proteinuria with hematuria; H = Hematuria

Table 2. Clinical progress of patients with IgMN at last follow-up.

Clinical manifestation	NS	PU	PUH	H	All patients
Number of patients	18	11	9	1	39
Median follow-up period (months)	24	31	27	29	25
Renal function					
Initially normal	16/18	5/11	8/9	1/1	30/39
Stable	16/18	9/11	9/9	1/1	36/39
Deteriorate	2/18	2/11	0/9	0/1	4/39
Proteinuria					
Stable	2/18	4/11	4/9	1/1	10/39
Increase	0/18	4/11	3/9	0/1	7/39
Decrease/remission	16/18	2/11	2/9	0/1	20/39

NS = nephrotic syndrome; PU = Proteinuria; PUH = Proteinuria with hematuria; H = Hematuria

The clinical progress of these 39 patients was depicted in table 2. Of the 18 patients with nephrotic syndrome, 16 (89%) were steroid responsive and 6 (33%) were steroid dependent. After a median follow-up period of 24 months, this group of nephrotic patients had stable renal function and normal blood pressure. Of the 11 patients with isolated proteinuria, six developed hypertension and four had impaired renal function after a median follow-up period of 31 months. Two of them had progressive deterioration in renal function while two other patients had spontaneous remission. For the mixed hematuria and proteinuria group, only one of the nine patients had mild hypertension after a median follow-up period of 27 months. One patient, who had a mildly impaired renal function at presentation, remained stable during the follow-up period. The patient with isolated hematuria had normal renal function during the follow-up period of 29 months.

DISCUSSION

IgMN is a glomerular disease defined by its immunopathologic features: the presence of IgM as the sole or dominant immunoglobulin deposited in the glomerular mesangial regions in a diffuse and generalized manner (3). Patients usually presented with nephrotic syndrome (3). However, they can also present with proteinuria and hematuria, isolated proteinuria and isolated hematuria (1,5,10). In a case series from Cohen (1,11), out of 29 patients suffering from IgMN, 23 (79%) had heavy proteinuria (greater than 3 g/day); nine had both proteinuria and microscopic hematuria, and six (20.6%) had isolated hematuria. In our series, most of our patients presented as nephrotic syndrome (46%). However, far fewer patients presented as isolated hematuria (3%) as compared with other studies. The discrepancy is likely related to sampling bias due to the difference in the indications of renal biopsy. In our center, we would not perform renal biopsy routinely for patients with isolated hematuria. In some other centers, renal biopsy would be done in all patients suspected of suffering from glomerular disease provided that no contraindications were present. The prevalence of patients with IgMN presented with isolated hematuria could be as high as 20% in these centers (12).

The existence of IgMN as a separate clinical entity and its clinical prognostic significance has always been a subject of controversy. Apparent transitions from minimal change disease to IgMN and from IgMN to focal segmental glomerulosclerosis in subsequent biopsy specimens have been reported (15-18). One hypothesis is that minimal change disease, IgMN and focal, and segmental glomerulosclerosis are not separate entities but simply represent a spectrum of disease that begins with minimal change and ends in focal sclerosis (10). An alternate view is that minimal change disease, IgMN and focal, and segmental glomerulosclerosis are three separate entities but having overlapping microscopic appearance (10). Evidence to support the consideration of IgMN as a different clinical entity includes the proposed difference in the pathogenesis of the disease (focal segmental glomerulosclerosis and minimal change disease are disorders of visceral epithelium while mesangial proliferative disease is a disorder of the mesangium); the presence of IgM deposit in the mesangium; and the differences in the clinical response to steroid therapy and clinical course from minimal change disease (11).

The nephrotic syndrome in IgMN was found to be corticosteroid resistant in 20% to 50% of patients (5, 12). Higher proportions of patients were steroid dependent (60 % vs 14%) and had poor response to cyclophosphamide (46% vs 100% were cyclophosphamide responsive) when compared with patients with minimal change disease (5,11). In our series, a high proportion of patients were steroid responsive (89%) but 33 % of the responders were steroid dependent. The steroid responsiveness of our patients is apparently not as satisfactory as those groups of patients with minimal change disease. Whether there is any correlation between the degree of mesangial hypercellularity and the clinical course and outcome is still a subject of controversy. While Allen et al (13) found that mesangial hypercellularity was associated with frequent relapse and unfavorable course, Cohen et al (11) could not see such a correlation. Hsu et al (14) in their series of 41 patients with IgM nephropathy pointed out that patients whose biopsy specimens were consistent with minimal change nephrotic syndrome had most favorable clinical course.

From our experience, more patients in the isolated proteinuria group had impaired renal function at the time of diagnosis. Two (10%) patients in this group also showed progressive deterioration in their renal function during the follow-up period while the renal function of the patients in all other groups remained stable. There have been several reports of cases with IgMN in which a histologic transformation from minimal change or mesangial proliferation to focal segmental glomerulosclerosis had taken place (12,16-18). Usually these were cases that had poor response to therapy, progressive increase in proteinuria and deterioration in renal function. Cohen (3) and Border (10) suggested that the focal sclerosis appearance represented the late stage of mesangial proliferative glomerulonephritis.

Border (10) proposed that at the beginning of mesangial

injury (glomerulonephritis), the resting mesangial cells appeared normal or to have minimal changes. After stimulation, the mesangial cells proliferated and increased the synthesis of mesangial matrix, which could accumulate and cause glomerulosclerosis. The difference in microscopic appearance represented the different stages of the disease and timing of the biopsy. Generally, patients who exhibited diffuse mesangial expansion and hypercellularity with prominent diffuse mesangial IgM deposition in the renal biopsy had a more unfavorable outcome (15).

Recent investigations found that mesangial cells can be stimulated to transform into cells resembling monocytes and macrophages and produce cytokines for cell proliferation and matrix expansion, for example, IL 1, IL 6, platelet derived growth factor, transforming growth factors ß (10,19,20). Such transformation can explain why immunologic or other stimuli can injure glomeruli by stimulating the mesangium to start a cycle of perpetual cell proliferation and matrix expansion that lead to sclerosis (10). This provides an insight on the possible pathogenesis of mesangial proliferative glomerulonephritis. Differences in the pathogenic mechanism should separate IgMN from idiopathic focal segmental glomerulosclerosis and minimal change glomerulonephritis. This is further supported by the differences in their clinical response to steroid therapy and the clinical course of the disease.

One patient with isolated hematuria was found to have the most favorable prognosis (3,10,11). This only patient showed a normal and stable renal function during the 29 months follow-up period. It seems that isolated hematuria represents a favorable clinical feature. It is possible that there are two unrelated disorders with initially rather similar histological pictures (12). One type usually associates with the nephrotic syndrome and shows a tendency to morphological change and development of impaired renal function. The other type manifests as hematuria with or without proteinuria and the overall clinical course is usually more favorable (12).

CONCLUSIONS

IgMN represents a different pathological-clinical entity from minimal change disease and focal segmental glomerulosclerosis. Nephrotic syndrome is the commonest manifestation in our series. In the group of patients presented with nephrotic syndrome, most of them were steroid responsive but a high percentage of them were steroid dependent. The patients in the mixed proteinuria and hematuria group appeared to have better prognosis than patients with isolated proteinuria. IgMN itself may represent two unrelated disorders with different long-term prognosis. Further studies on the pathophysiology of the disease, the different presentations of the disorder, the clinical course and response to treatment are warranted.

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